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ORIGINAL ARTICLE

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Bone mineral density improves during 2 years of treatment with bisphosphonates in patients with ankylosing spondylitis

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Aims: To evaluate whether 2 years of treatment with bisphosphonates in combination with calcium/vitamin D supplements has an effect on lumbar spine and hip bone mineral density (BMD) in ankylosing spondylitis (AS) patients starting tumour necrosis factor-α inhibitors or receiving conventional treatment. Secondly, to explore the development of radiographic vertebral fractures.

Methods: Patients from the Groningen Leeuwarden AS cohort receiving bisphosphonates based on clinical indication and available 2-year follow-up BMD measurements were included. BMD of lumbar spine (L1–L4) and hip (total proximal femur) were measured using dual-energy X-ray absorptiometry. Spinal radiographs (Th4–L4) were scored for vertebral fractures according to the Genant method.

Results: In the 20 included patients (median 52 years, 14 males), lumbar spine and hip BMD Z-scores increased significantly; median from −1.5 (interquartile range [IQR] −2.2 to 0.4) to 0.1 (IQR −1.5 to 1.0); $P < .001$ and median from −1.0 (IQR −1.6 to −0.7) to −0.8 (IQR −1.2 to 0.0); $P = .006$ over 2 years, respectively. In patients also treated with tumour necrosis factor-α inhibitors ($n = 11$), lumbar spine and hip BMD increased significantly (median 2-year change +8.6% [IQR 2.4 to 19.6; $P = .009$] and +3.6% [IQR 0.7–9.0; $P = .007$]). In patients on conventional treatment ($n = 9$), lumbar spine BMD increased significantly (median 2-year change +3.6%; IQR 0.7 to 9.0; $P = .011$) and no improvement was seen in hip BMD (median −0.6%; IQR −3.1 to 5.1; $P = .61$). Overall, younger AS males with limited spinal radiographic damage showed most improvement in lumbar spine BMD. Four mild radiographic vertebral fractures developed in 3 patients and 1 fracture increased from mild to moderate over 2 years in postmenopausal women and middle-aged men.

Conclusion: This explorative observational cohort study in AS showed that 2 years of treatment with bisphosphonates in combination with calcium/vitamin D supplements significantly improves lumbar spine BMD. Mild radiographic vertebral fractures still occurred.

The authors confirm that the PI for this paper is Dr. Anneke Spoorenberg and that she had direct clinical responsibility for patients.

KEYWORDS

ankylosing spondylitis, bisphosphonates, bone mineral density, tumour necrosis factor-α inhibitors, vertebral fractures

1 | INTRODUCTION

Ankylosing spondylitis (AS) is a chronic rheumatic inflammatory disease, which mainly affects the axial skeleton. Besides spinal osteoproliferation, excessive bone loss is a major complication of AS. Low bone mineral density (BMD), especially at the lumbar spine, can already be observed at a relatively young age.[1,2] Acute inflammatory lesions on sacroiliac joint magnetic resonance imaging were found to be associated with low BMD.[3] Vertebral fractures are the most important outcome of excessive bone loss and are frequently present in AS patients.[1,4]

The main cause of primary osteoporosis is age-related bone loss in postmenopausal women. Secondary osteoporosis results from the presence of other diseases or conditions that predisposes to bone loss and occurs in both males and females. Currently, there are no clear guidelines for the evaluation of bone loss and the treatment of secondary osteoporosis in patients with AS. In daily clinical practice, secondary osteoporosis is often treated according to the same guidelines as primary osteoporosis, although AS mainly affects males at relatively young age. This antiosteoporotic treatment consists of bisphosphonates in combination with calcium/vitamin D supplements.

Several studies in AS investigated the anti-inflammatory effect of bisphosphonates.[5–10] However, follow-up data regarding the effect of bisphosphonates on BMD are scarce and data about the effect on vertebral fractures are lacking. There is 1 open-label study in AS patients with active disease that showed a significant improvement in absolute BMD scores at the lumbar spine after 6 months of treatment with neridronate, which was not observed at the hip.[8] Another retrospective study in AS patients with spinal pain intensity score >4 (on a scale of 0–10) did not show beneficial effect on lumbar spine or hip BMD after 6 months treatment with alendronate.[11]

Nowadays, tumour necrosis factor-α (TNF-α) inhibitors are prescribed to control disease activity, with good long-term adherence in daily clinical practice.[12] These agents also have proven to have an effect on BMD. A large randomized controlled trial found a significant increase in BMD at the lumbar spine and hip after 6 months of infliximab compared with placebo. Open-label extension showed further improvement in BMD after 2 years of infliximab.[13] Multiple observational studies reported a continuous improvement in BMD at the lumbar spine and, to a lesser extent, at the hip after long-term treatment with TNF-α inhibitors.[1,14]

The aim of the present study was to evaluate whether 2 years of treatment with bisphosphonates in combination with calcium/vitamin D supplements has an effect on lumbar spine and hip BMD in AS patients starting TNF-α inhibitors or receiving conventional treatment in daily clinical practice. Secondly, to explore the development of radiographic vertebral fractures in these patients.

What is already known about this subject

- Osteoporosis and vertebral fractures occur in hip ankylosing spondylitis (AS) patients at relatively young age.
- In daily clinical practice, treatment with bisphosphonates is often applied in AS, but scientific studies with >6 months follow-up regarding the effect on bone mineral density (BMD) and vertebral fractures are lacking.

What this study adds

- Lumbar spine BMD improved significantly during 2 years of bisphosphonates, which was most pronounced in younger AS males with limited spinal radiographic damage.
- Hip BMD only improved significantly in patients also treated with tumour necrosis factor-α inhibitors.
- Mild radiographic vertebral fractures still occurred in postmenopausal women and middle-aged men. Most fractures were observed in patients who already had vertebral fractures and who were also treated with tumour necrosis factor-α inhibitors because of persistent active disease.

2 | METHODS

The Groningen Leeuwarden AS (GLAS) cohort is an ongoing prospective observational cohort study which started at the end of 2004 in the north of the Netherlands (principal investigator: Dr A. Spoorenberg). For the present analysis, patients fulfilling the modified New York criteria for AS, who were treated with bisphosphonates in combination with calcium and/or vitamin D supplements and had available 2-year follow-up BMD measurements were included. The antiosteoporotic treatment was started based on clinical indication according to the treating physician.

The GLAS cohort was approved by the local ethics committees of the Medical Center Leeuwarden (MCL) and University Medical Center Groningen (UMCG). All patients provided written informed consent according to the Declaration of Helsinki.

2.1 | Assessments of bone loss

2.1.1 | BMD

At first visit and after 2 years of follow-up, BMD at the lumbar spine (anterior–posterior projection at L1–L4) and hip (total proximal femur) were measured using the same dual-energy X-ray absorptiometry machine within patients (Hologic QDR Discovery for UMCG patients and Hologic QDR Delphi for MCL patients, Waltman, MA, USA). Coefficient of variation (CV) and least significant change were evaluated automatically using Hologic software. CV for total BMD was reported to be 1.0%, least significant change was reported to be 0.022 g/cm^2 for lumbar spine BMD and 0.027 g/cm^2 for hip BMD. Lumbar vertebrae showing fractures were excluded from the BMD measurement. Z-scores, the number of standard deviations from the normal mean corrected for age and sex, were calculated using the NHANES reference database. The International Society for Clinical Densitometry recommends using BMD Z-scores instead of BMD T-scores in premenopausal women and men younger than 50 years.[15]

2.1.2 | Vertebral fractures

Lateral radiographs of the thoracic and lumbar spine were scored for radiographic vertebral fractures by 2 independent readers blinded for patient characteristics.[4] According to the method of Genant *et al*., anterior, middle and posterior heights of the vertebra Th4–L4 were assessed. Fractures were categorized as mild (≥20–<25% height reduction), moderate (≥25–<40% height reduction) or severe (≥40% height reduction).

2.2 | Other assessments

At the same time points, serum levels of 25-hydroxyvitamin D (25OHvitD) were measured by radioimmunoassay (DiaSorin, Stillwater, MN, USA; inter assay coefficient of variation IE-CV) 14–15%; UMCG until June 2010 and MCL until July 2008), ECLIA (Modular Analytics E170, Roche Mannheim, Germany; IE-CV 12–13%; MCL July 2008 until 2011), or automated liquid chromatography–mass spectrometry method (IE-CV 4–5%; UMCG since 2010 and MCL since 2011). Disease activity was assessed using AS disease activity score, Bath AS disease activity index and C-reactive protein (measured during routine diagnostic patient care; IE-CV < 5%). Lateral radiographs of the cervical and lumbar spine were scored for spinal radiographic damage by 2 independent readers using the modified Spine AS score (mSASSS).[4]

2.3 | Statistical analysis

Results were expressed as number of patients (%) or median (interquartile range [IQR]) for categorical and continuous data, respectively. Fisher's Exact and Mann–Whitney U tests were used to compare patient characteristics between groups. Wilcoxon-signed rank test was used to compare assessments at first visit and after 2 years of follow-up. Analyses were stratified for starting treatment with TNF-α inhibitors or receiving conventional treatment (nonsteroidal anti-inflammatory drugs). P-values ≤0.05 were considered as statistically significant. Statistical analysis was performed with IBM SPSS Statistics 23 (SPSS, Chicago, IL, USA).

3 | RESULTS

Of the 20 included AS patients, 11 were treated with risedronate (35 mg/wk), 7 with alendronate (70 mg/wk), 1 with intravenous pamidronate (60 mg) and 1 with etidronic acid–calcium carbonate. In the majority of patients, antiosteoporotic treatment was started because of osteoporosis. Other reasons were systemic steroid use or the presence of osteopenia and vertebral fractures. Eleven (55%) patients started TNF-α inhibitors because of active disease (10 continued this treatment for 2 y) and the other 9 (45%) received conventional treatment for AS symptoms. Patient characteristics at first visit and type of bisphosphonate used in both treatment groups are presented in Table 1.

Seventeen (85%) patients used bisphosphonates during the entire 2-year follow-up within the GLAS cohort (TNF-α inhibitor group: *n* = 9, conventional treatment group: *n* = 8). Thirteen (65%) patients started treatment with bisphosphonates median 3.1 years before inclusion in the GLAS cohort (TNF-α inhibitor group: n = 9, median 3.1 y, conventional treatment group: *n* = 4, median 3.8 y).

As expected, all disease activity assessments were significantly higher in patients starting TNF-α inhibitors. Furthermore, physical function was worse and serum levels of 25-hydroxyvitamin D were lower. Disease severity expressed by spinal radiographic damage (mSASSS) was similar in both treatment groups. Also lumbar spine and hip BMD were comparable between both groups, although radiographic vertebral fractures were more often found in patients starting TNF-α inhibitors.

3.1 | Change in BMD over 2 years

In the total group, treatment with bisphosphonates in combination with calcium/vitamin D supplements significantly improved lumbar spine and hip BMD; median lumbar spine BMD Z-score increased from −1.5 at first visit to 0.1 after 2 years ($P < .001$) and median hip BMD Z-score from −1.0 at first visit to −0.8 after 2 years ($P = .006$). Similar results were found for BMD T-scores (data not shown).

In the 11 patients starting TNF-α inhibitors, lumbar spine BMD increased significantly (Figure 1A); median change in Z-score was 0.7 (IQR 0.3 to 1.4) and in absolute BMD 8.6% (IQR 2.4 to 19.6). Also hip BMD increased significantly (Figure 1B); median change in Z-score was 0.3 (IQR 0.2 to 0.6) and in absolute BMD 3.6% (IQR 1.5 to 7.8).

TABLE 1 Characteristics of the AS study population treated with bisphosphonates in combination with calcium/vitamin D supplements, stratified for the use of TNF-α inhibitors

	All patients (*n* = 20)	Patients starting TNF-α inhibitors (*n* = 11)	Patients on conventional treatment (*n* = 9)
Male sex	14 (70)	7 (64)	7 (78)
Age (y)	52 (46 to 64)	57 (45 to 65)	50 (46 to 61)
Duration of symptoms (y)	27 (8 to 40)	20 (8 to 44)	29 (15 to 39)
Time since diagnosis (y)	7 (4 to 28)	8 (5 to 28)	6 (1 to 31)
HLA-B27+	15 (75)	6 (55)	9 (100)*
NSAID use	13 (65)	5 (46)	8 (89)
Systemic steroid use	3 (15)	1 (9)'	2 (22)″
$ASDAS_{CRP}$	3.6 (2.2 to 4.4)	4.2 (3.5 to 4.6)	2.1 (1.8 to 3.5)*
BASDAI (range 0–10)	5.3 (2.8 to 7.3)	5.8 (5.0 to 8.0)	3.8 (1.9 to 5.5)*
CRP (mg/l)	15 (4 to 23)	19 (10 to 24)	5 (2 to 15)*
BASFI (range 0–10)	7.2 (3.8 to 7.9)	7.6 (7.1 to 8.5)	3.9 (1.3 to 7.3)*
LS BMD Z-score	−1.5 (−2.2 to 0.4)	−0.8 (−2.3 to 0.6)	−1.6 (−2.8 to 0.0)
LS BMD Z-score ≤−1	10 (53)	5 (50)	5 (56)
LS BMD Z-score ≤−2	6 (32)	3 (30)	3 (33)
Hip BMD Z-score	−1.0 (−1.6 to −0.7)	−1.0 (−1.8 to −0.8)	−1.0 (−1.5 to 0.1)
Hip BMD Z-score ≤−1	11 (58)	7 (64)	4 (50)
Hip BMD Z-score ≤−2	1 (5)	1 (9)	0 (0)
25OHvitD (nmol/L)	66 (36 to 89)	38 (29 to 70)	89 (55 to 96)*
Radiographic VF[a]	7 (41)	6 (60)†	1 (14)‡
mSASSS (range 0–72)[b]	6.0 (2.9 to 42.3)	14.2 (3.4 to 33.7)	5.2 (1.6 to 63.2)
Type of bisphosphonate treatment			
Risedronate	11 (55)	6 (55)	5 (56)
Alendronate	7 (35)	3 (27)	4 (44)
Intravenous pamidronate	1 (5)	1 (9)	0 (0)
Etidronic acid-calcium carbonate	1 (5)	1 (9)	0 (0)

Values are number (%) of patients or median (interquartile range).
[a]Radiographs of the thoracic and lumbar spine could be scored in 17 patients. [b] Radiographs of the cervical and lumbar spine could be scored in 14 patients.
*$P < .05$ compared to patients starting TNF-α inhibitors.
'prednison (5 mg/d);
″budenofalk (3 and 6 mg/d).
†16 vertebral fractures (9 mild, 5 moderate, 2 severe) in 6 patients;
‡1 vertebral fracture (mild) in 1 patientAS: ankylosing spondylitis; TNF-α: tumour necrosis factor-α; HLA-B27+: human leukocyte antigen B27 positive; ASDAS: AS disease activity score; BASDAI: Bath AS disease activity index; CRP: C-reactive protein; BASFI: Bath AS functional index; LS: lumbar spine; BMD: bone mineral density; 25OHvitD: 25-hydroxyvitamin D; VF: vertebral fracture; mSASSS: modified stoke AS spinal score; NSAID, nonsteroidal anti-inflammatory drug.

In the 9 patients on conventional treatment, lumbar spine BMD increased significantly (Figure 1C); median change in Z-score was 0.4 (IQR 0.2 to 0.7) and in absolute BMD 3.6% (IQR 0.7 to 9.0). No significant improvement in hip BMD was found (Figure 1D); median change in Z-score was 0.1 (IQR −0.2 to 0.3) and in absolute BMD −0.6% (IQR −3.1 to 5.1).

Overall, improvement in lumbar spine BMD of ≥0.5 Z-score was found in males (82%) of relatively young age (median 45 years) and limited spinal radiographic damage (median 4.3 mSASSS units).

3.2 | Development of vertebral fractures

During 2-year follow-up, 4 new radiographic vertebral fractures were found in 3 of the 17 (18%) patients. In patients with TNF-α inhibitors, 3 mild fractures occurred in 2 postmenopausal females (67 and 68 years). In addition, 1 existing fracture increased in severity from mild to moderate in 1 male (48 years). In patients on conventional treatment, 1 new mild fracture was observed in 1 male (51 years). None of these fractures received clinical attention. More

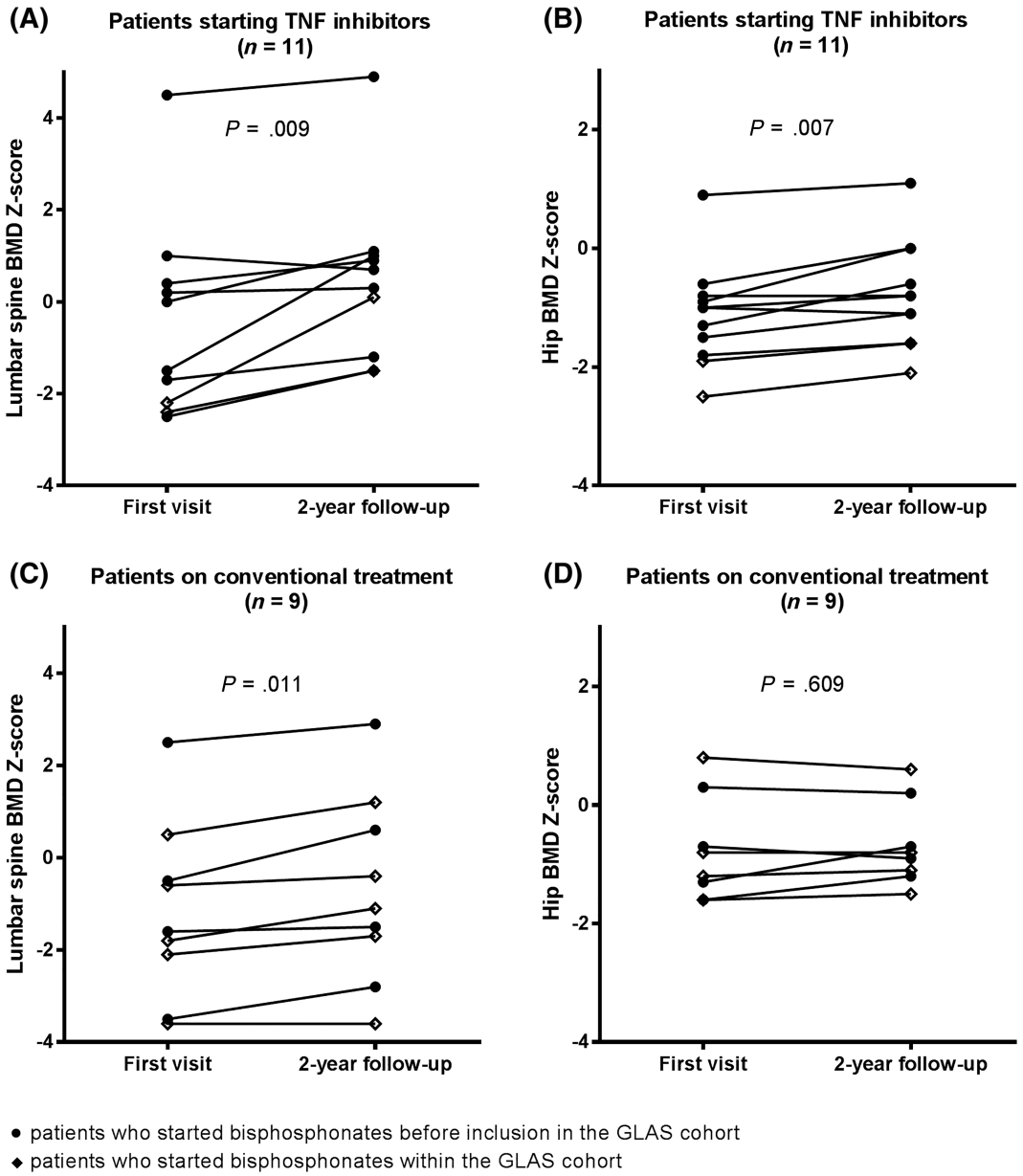

FIGURE 1 Lumbar spine and hip bone mineral density (BMD) Z-scores during 2 years of treatment with bisphosphonates in combination with calcium/vitamin D supplements in 20 ankylosing spondylitis patients, stratified for the use of tumour necrosis factor-α inhibitors. GLAS, Groningen Leeuwarden ankylosing spondylitis

details about the characteristics and treatment of these patients are presented in Table 2.

3.3 | Other assessments over 2 years

There was no significant change in serum levels of 25-hydroxyvitamin D over 2 years (Table 3). Disease activity decreased significantly in both groups; median improvement in AS disease activity score was 2.1 for patients starting TNF-α inhibitors and 0.4 for patients on conventional treatment. Overall, spinal radiographic progression was relatively low. Median progression in mSASSS was 1.4 (IQR 0.5 to 1.6) and 0.0 (IQR 0.0 to 0.4) in these 2 treatment groups, respectively. Two patients developed 1 new syndesmophyte in the TNF-α inhibitor group compared to none in the conventional treatment group.

4 | DISCUSSION

The present study evaluated whether 2 years of treatment with bisphosphonates in combination with calcium/vitamin D supplements has an effect on lumbar spine and hip BMD in established AS patients from daily clinical practice. BMD improved significantly during treatment with bisphosphonates, as was shown in other small studies.[8,16] The median change in absolute BMD scores after 2 years of bisphosphonates was +8.6 and +3.6% at the lumbar spine and +3.6

TABLE 2 Characteristics and treatment of AS patients with new vertebral fractures (n = 3) or increase in severity (n = 1) during 2 years of follow-up

	Patient 1	Patient 2	Patient 3	Patient 4
Development of VF + site	New: Th12 and L3 grade 1, biconcave	New: Th12 grade 1, biconcave	Increase in severity: Th11 grade 2, wedge	New: Th8 grade 1, biconcave
Sex, age	Female, 67 y	Female, 67 y	Male, 48 y	Male, 51 y
Bisphosphonate treatment, % of time used	Pamidronate 60 mg/12 wk, 100%	Alendronate 70 mg/wk, 100%	Risedronate 35 mg/wk, 100%	Alendronate 70 mg/wk, 100%
Anti-TNF treatment, % of time used	Adalimumab 40 mg/2 wk, 84% (stopped)	Etanercept 50 mg/wk, 100%	Infliximab, 300 mg/8 wk, 100%	No
Presence of VF at baseline + site	Th9, Th10 grade 2, Th11 grade 3, biconcave	Th7 grade 1, wedge, Th9 grade 2, Th11 grade 3, biconcave	Th9, Th10, Th11, Th12 grade 1, wedge	No
BMD LS Z-score baseline *vs* 2 y	N/A	−2.2 *vs* 0.1	−2.5 *vs* -1.5	−1.8 *vs* -1.1
BMD hip Z-score baseline *vs* 2 y	−0.9 *vs* 0.0	−1.9 *vs* -1.6	−1.8 *vs* -1.6	−1.2 *vs* -1.1
ASDAS baseline *vs* 2 y	4.41 *vs* 3.82	3.52 *vs* 2.72	4.60 *vs* 2.26	1.87 *vs* 1.42

See Table 1 for abbreviations

and −0.6% at the hip, respectively, in patients starting treatment with TNF-α inhibitors or receiving conventional treatment. Interestingly, in both groups, most improvement in lumbar spine BMD was found in younger males with limited spinal radiographic damage. Previously, a retrospective cohort study compared BMD change over approximately 1-year in 4 groups of AS patients on conventional treatment (n = 40), bisphosphonates plus conventional treatment (n = 20), TNF-α inhibitors (n = 19) and bisphosphonates plus TNF-α inhibitors (n = 11). They reported that BMD improvement at the greater trochanter of the hip was most pronounced in patients receiving bisphosphonates in combination with TNF-α inhibitors.[16] An open-label study including AS patients with active disease (Bath AS disease activity index ≥4) investigated BMD as secondary outcome during 6 months of treatment with high intravenous doses of the amino-bisphosphonate neridronate (n = 30) or infliximab (n = 30). In line with our findings, they showed that bisphosphonates resulted in a significant increase in absolute BMD scores at the lumbar spine (mean improvement 4.3%), but not at the hip (mean improvement 0.1–2.2%).[8] In contrast to our and other studies with TNF-α inhibitors,[12,16–18] they reported that infliximab had no significant effect on BMD. Unfortunately, no further analysis or discussion was provided. Supporting our data and those of other studies, a meta-analysis including 568 AS patients from 1 randomized controlled trial and 7 observational studies consistently demonstrated that lumbar spine and total hip BMD increased significantly with 8.6 and 2.5%, respectively, after 2 years of treatment with TNF-α inhibitors.[14]

Bisphosphonates and TNF-α inhibitors influence the bone metabolism differently. Bisphosphonates have an inhibitory effect on bone resorption by chemical adsorption to hydroxyapatite and/or a direct effect on osteoclast activity.[19,20] The underlying pathophysiological mechanism of TNF-α inhibitors on the bone metabolism is not yet completely understood, but most likely involves the Wnt signaling pathway, which affects both osteoclasts and osteoblasts activity.[21] A recent cross-sectional study including 71 AS patients showed that higher serum levels of Dickkopf-1, a natural inhibitor of the Wnt pathway, were associated with lower lumbar spine BMD and prevalent radiographic vertebral fractures. This indicates that high levels of Dickkopf-1 are related to the severity of bone loss in AS.[22]

Besides the effect of bisphosphonates on BMD, we also explored the development of radiographic vertebral fractures, the most important clinical outcome reflecting bone loss of the spine. At first visit, 17 mild to severe vertebral fractures were found in 7 (41%) patients. During 2 years, 4 mild vertebral fractures developed in 3 (18%) patients and 1 existing fracture increased from mild to moderate. The majority of prevalent and incident vertebral fractures were found in patients with active disease, starting treatment with TNF-α inhibitors. This can probably be explained by persistently high disease activity (before the start of TNF-α inhibitors), lower serum levels of vitamin D and worse physical function in these AS patients. New radiographic vertebral fractures occurred in postmenopausal women and middle-aged men. Three out of these 4 patients already had multiple vertebral fractures.

The present study is the first to explore the development of vertebral fractures in AS patients with a clinical indication for antiosteoporotic treatment. In our larger observational study on vertebral fractures, 39 (21%) of the 184 AS patients starting TNF-α inhibitors already had radiographic vertebral fractures at baseline, 9 (5%) developed new vertebral fractures and 7 (4%) showed an increase in severity of existing factures after 2 years of follow-up.[4] Another observational study in 49 AS patients starting etanercept reported that the number of patients with radiographic vertebral fractures increased from 6 (12%) at baseline to 15 (31%) after 2 years.[23]

For the present analysis, we selected patients who were treated with bisphosphonates and had available 2-year follow-up BMD measurements. As expected, this subgroup of patients was older (median 52 *vs* 43 y), had longer duration of AS symptoms (median

TABLE 3 Clinical assessments at first visit and after 2 years of follow-up in AS patients treated with bisphosphonates in combination with calcium/vitamin D supplements, stratified for the use of TNF-α inhibitors

	First visit	2 years	*P*-value
Patients starting TNF-α inhibitors (n = 11)			
LS BMD Z-score	−0.8 (−2.3 to 0.6)	0.5 (−1.3 to 1.0)	.009
Hip BMD Z-score	−1.0 (−1.8 to −0.8)	-0.8 (−1.6 to 0.0)	.007
25OHvitD (nmol/L)	38 (29 to 70)	58 (46 to 66)	.726
$ASDAS_{CRP}$	4.2 (3.5 to 4.6)	2.3 (1.1 to 3.8)	.008
BASDAI (range 0–10)	5.8 (5.0 to 8.0)	2.2 (1.0 to 6.2)	.014
CRP (mg/l)	19 (10 to 24)	3 (2 to 12)	.026
mSASSS (range 0–72)	14.2 (3.4 to 33.7)	15.8 (4.5 to 34.8)	.042
Patients on conventional treatment (n = 9)			
LS BMD Z-score	−1.6 (−2.8 to 0.0)	−1.1 (−2.3 to 0.9)	.011
Hip BMD Z-score	−1.0 (−1.5 to 0.1)	−0.9 (−1.2 to 0.0)	.609
25OHvitD (nmol/L)	89 (55 to 96)	69 (52 to 88)	.686
$ASDAS_{CRP}$	2.1 (1.8 to 3.5)	1.6 (1.4 to 2.9)	.021
BASDAI (range 0–10)	3.8 (1.9 to 5.5)	2.8 (1.8 to 4.7)	.141
CRP (mg/l)	5 (2 to 15)	3 (2 to 8)	.026
mSASSS (range 0–72)	5.2 (1.6 to 63.2)	6.4 (2.0 to 63.2)	.180

See Table 1 for abbreviations.

27 *vs* 16 y), lower BMD (median lumbar spine Z-score −1.5 *vs* −0.4, hip Z-score −1.0 *vs* −0.2) and more often radiographic vertebral fractures (41 *vs* 20%) in comparison with the total study population from the GLAS cohort.[4]

The present study is based on real life data. The antiosteoporotic treatment was started based on clinical indication according to the treating physician, mainly the presence of osteoporosis. Unfortunately, the Fracture Risk Assessment Tool score was not yet available in these patients. A limitation of our study is that the effect of bisphosphonates on BMD may be underestimated since 65% of the patients started treatment with bisphosphonates before inclusion in the GLAS cohort (median 3.1 y). An open-label extension study in postmenopausal women showed that continuous alendronate treatment for 7 years increased BMD, but the largest increase was observed during the first 3 years of treatment.[24]

It is known that the anterior–posterior view of the lumbar spine DXA can be overestimated by the presence of syndesmophytes.[25,26] Since mSASSS progression was relatively low and the large majority of patients did not develop new syndesmophytes over 2 years, it can be assumed that there was no influence of spinal osteoproliferation on the 2-year improvement in lumbar spine BMD. Moreover, young AS males with limited spinal radiographic damage showed most improvement in lumbar spine BMD. We do realize that a larger number of patients, long-term follow-up, and a control group are needed to investigate and detect a potential extra increase in spinal radiographic damage due to the treatment effect of bisphosphonates on bone formation in AS.

In conclusion, the results from this observational cohort study in daily clinical practice show that treatment with bisphosphonates in combination with calcium/vitamin D supplements improves BMD over 2 years in established AS patients. Lumbar spine BMD improved significantly, which was most pronounced in younger AS males with limited spinal radiographic damage. Hip BMD only improved significantly in patients also starting TNF-α inhibitors. Our finding that the effect of treatment was most pronounced in the lumbar spine corresponds to the disease process in AS since disease activity is predominantly observed in the axial skeleton.

This is the first study exploring the occurrence of radiographic vertebral fractures in AS patients with low BMD and/or vertebral fractures at baseline treated with bisphosphonates. Mild radiographic vertebral fractures still occurred in postmenopausal women and middle-aged men. Most fractures were observed in patients who already had vertebral fractures and who were also treated with TNF-α inhibitors because of persistent active disease. Due to the small number and differences in disease activity at baseline, it is difficult to put the incidence rate into perspective. Since fractures are regarded as the most important outcome of bone fragility, larger studies with long-term follow-up are needed to further investigate the effect of bisphosphonates and calcium/vitamin D supplements not only on BMD but also on vertebral fractures in AS.

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COMPETING INTERESTS

S.A. has received research grants from Pfizer. F.W. has received consulting fees from Abbvie. A.S. has received research grants from Abbvie, Pfizer, UCB and Novartis, and consulting fees from Abbvie, Pfizer, MSD, UCB, and Novartis. The other authors declare that they have no competing interests.

CONTRIBUTORS

S.A. participated in the design of the study, performed the statistical analysis and interpretation of data, and drafted the manuscript. F.W. and R.B. performed the acquisition of clinical data and critically revised the manuscript. J.V. contributed to the to the acquisition,

statistical analysis and interpretation of data, and critically revised the manuscript. E.R., E.V. and F.M. participated in the design of the study, contributed to the interpretation of data and critically revised the manuscript, AS participated in the design of the study, performed the acquisition of clinical data, contributed to the interpretation of data and critically revised the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data were obtained within the GLAS cohort, which was approved by the local ethics committees of the MCL and UMCG. All patients provided written informed consent according to the Declaration of Helsinki.

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